L1

L2

L3

L4

(FILE 'HOME' ENTERED AT 11:59:34 ON 04 DEC 2002)

FILE 'REGISTRY' ENTERED AT 12:05:09 ON 04 DEC 2002 1 S 9076-63-5/RN

FILE 'CAOLD, CAPLUS, CASREACT, CROPU, DGENE, DPCI, ENCOMPPAT, ENCOMPPAT2, EUROPATFULL, IFIPAT, INPADOC, JAPIO, PAPERCHEM2, PATDD, PATDPA, PATOSDE, PATOSEP, PATOSWO, PCTFULL, PIRA, RAPRA, SYNTHLINE, TULSA, TULSA2, USPATFULL, USPAT2, WPIDS' ENTERED AT 12:05:23 ON 04 DEC 2002

FILE 'REGISTRY' ENTERED AT 12:05:31 ON 04 DEC 2002 SET SMARTSELECT ON

SEL L1 1- CHEM : 4 TERMS SET SMARTSELECT OFF

FILE 'CAOLD, CAPLUS, CASREACT, CROPU, DGENE, DPCI, ENCOMPPAT, ENCOMPPAT2, EUROPATFULL, IFIPAT, INPADOC, JAPIO, PAPERCHEM2, PATDD, PATDPA, PATOSDE, PATOSEP, PATOSWO, PCTFULL, PIRA, RAPRA, SYNTHLINE, TULSA, TULSA2, USPATFULL, USPAT2, WPIDS' ENTERED AT 12:05:32 ON 04 DEC 2002

- 9 S L2
- 9 DUP REM L3 (0 DUPLICATES REMOVED)
- L5 3 S L3 (L) (DNA OR CDNA OR NUCLEOTIDE OR POLYNUCLEOTIDE OR NUCLE

L5 'ANSWER 1 OF 3 CAPLUS COPYRIGHT 2002 ACS

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ACCESSION NUMBER:
                         2000:117169 CAPLUS
DOCUMENT NUMBER:
                         132:162810
TITLE:
                         Cloning of genes for L-lysine-2-oxoglutarate
                         6-aminotransferase and piperidine-6-carboxylate
                         dehydrogenase from Flavobacterium lutescens and use of
                         the genes for production of L-homoglutamic acid
INVENTOR (S):
                         Fujii, Tadashi; Narita, Takao; Nakata, Kuniho;
                         Agematu, Hitosi; Tsunekawa, Hiroshi; Isshiki, Kunio;
                         Yoshioka, Takeo
PATENT ASSIGNEE(S):
                         Mercian Corp., Japan
SOURCE:
                         PCT Int. Appl., 62 pp.
                         CODEN: PIXXD2
DOCUMENT TYPE:
                         Patent
                         Japanese
LANGUAGE:
FAMILY ACC. NUM. COUNT:
PATENT INFORMATION:
     PATENT NO.
                  KIND DATE
                                         APPLICATION NO. DATE
                     ----
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                                          -----
     WO 2000008170 A1 20000217
                                         WO 1999-JP4197 19990804
         W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU,
             CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN,
             IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK,
             MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ,
             TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ,
             MD, RU, TJ, TM
         RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK,
             ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG,
             CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
     CA 2337981
                           20000217
                      AA
                                          CA 1999-2337981 19990804
     AU 9950642
                      A1
                           20000228
                                          AU 1999-50642
                                                           19990804
     EP 1103612
                      A1
                           20010530
                                          EP 1999-935047
                                                           19990804
         R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
             IE, SI, LT, LV, FI, RO
PRIORITY APPLN. INFO.:
                                       JP 1998-232382
                                                       A 19980805
                                       JP 1999-182362 A 19990628
                                       WO 1999-J9
                                                   990419W 19990804
                                       WO 1999-JP4197
                                                       W 19990804
AB
     The genes encoding L-lysine-2-oxoglutarate 6-aminotransferase (LAT) and
     piperidine-6-carboxylate (P6C) dehydrogenase are isolated from
     Flavobacterium lutescens strain IFO 3084 and used for the transformation
     of F. lutescens to increase the yield of L-homoglutamic acid. LAT and P6C
     dehydrogenase are comprised of 491 and 510 amino acids, resp.
     Transformation of F. lutescens with the gene for LAT or P6C dehydrogenase
     increased the yield of L-homoglutamic acid by 1.5-2 folds.
REFERENCE COUNT:
                        13
                              THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS
                              RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT
      ANSWER 2 OF 3
                        PCTFULL
                                  COPYRIGHT 2002 Univentio
ACCESSION NUMBER:
                       2001092523 PCTFULL ED 20020826
                       NOVEL HUMAN POLYNUCLEOTIDES AND POLYPEPTIDES ENCODED
TITLE (ENGLISH):
                       THEREBY
                       NOUVEAUX POLYNUCLEOTIDES HUMAINS ET POLYPEPTIDES CODES
TITLE (FRENCH):
                       PAR CEUX-CI
INVENTOR (S):
                       SHIMKETS, Richard, A.; LEACH, Martin, D.
PATENT ASSIGNEE(S):
                       CURAGEN CORPORATION; SHIMKETS, Richard, A.; LEACH,
                       Martin, D.
DOCUMENT TYPE:
                       Patent
PATENT INFORMATION:
                       NUMBER
                                          KIND
                                                  DATE
                       WO 2001092523
                                           A2 20011206
                       AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR
DESIGNATED STATES
                       CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL
                       IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG
                       MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ
```

CF CG CI CM GA GN GW ML MR NE SN TD TG

APPLICATION INFO.: WO 2001-US10836 A 20010529 PRIORITY INFO.: US 2000-60/206,132 20000530 US 2000-60/228,716 20000829

ABEN The present invention provides ORFX, a novel isolated polypeptide, as well as a polynucleotide encoding ORFX and antibodies that

immunospecifically bind to ORFX or any derivative, variant, mutant, or fragment of the ORFX polypeptide, polynucleotide or antibody. The invention additionally provides methods in which the ORFX polypeptide,

polynucleotide and antibody are used in detection and treatment of a broad range of pathological states, as well as to other uses.

ABFR La presente invention concerne le polypeptide ORFX, nouveau polypeptide isole, ainsi qu'un polynucleotide codant pour le polypeptide ORFX et des anticorps qui se fixent de facon immunospecifique a ORFX ou a n'importe quel derive, variant, mutant ou fragment de ce polypeptide ORFX, de ce polynucleotide ou de cet anticorps. Cette invention concerne aussi des techniques dans lesquelles le polypeptide ORFX, le polynucleotide et l'anticorps sont utilises pour detecter et traiter un grand nombre d'etats pathologiques, ainsi que d'autres utilisations.

L5 ANSWER 3 OF 3 USPATFULL

ACCESSION NUMBER: 2002:235434 USPATFULL

TITLE: Biosensors, reagents and diagnostic applications of

directed evolution

INVENTOR(S): Minshull, Jeremy, Menlo Park, CA, UNITED STATES

Davis, S. Christopher, San Francisco, CA, UNITED STATES

Welch, Mark, Fremont, CA, UNITED STATES

Raillard, Sun Ai, Mountain View, CA, UNITED STATES

Vogel, Kurt, Palo Alto, CA, UNITED STATES

Krebber, Claus, Mountain View, CA, UNITED STATES

PATENT ASSIGNEE(S): Maxygen, Inc., Redwood City, CA (U.S. corporation)

NUMBER KIND DATE
----US 2002127623 A1 20020912
US 2001-920607 A1 20010731 (9)

NUMBER DATE

US 2000-222056P 20000731 (60)

US 2000-244764P 20001031 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION

LEGAL REPRESENTATIVE: LAW OFFICES OF JONATHAN ALAN QUINE, P O BOX 458.

ALAMEDA, CA, 94501

NUMBER OF CLAIMS: 130 EXEMPLARY CLAIM: 1

PATENT INFORMATION:

APPLICATION INFO.:

PRIORITY INFORMATION:

NUMBER OF DRAWINGS: 7 Drawing Page(s)

LINE COUNT: 6877

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Methods for sensing test stimuli using arrays of biopolymers are provided. Libraries of biopolymers, such nucleic acid variants, and expression products encoded by nucleic acid variants are provided. Reusable library arrays, and methods for their use are provided.

L4 'ANSWER 1 OF 9 USPATFULL

ACCESSION NUMBER: 2002:235434 USPATFULL

TITLE: Biosensors, reagents and diagnostic applications of

directed evolution

INVENTOR(S): Minshull, Jeremy, Menlo Park, CA, UNITED STATES

Davis, S. Christopher, San Francisco, CA, UNITED STATES

Welch, Mark, Fremont, CA, UNITED STATES

Raillard, Sun Ai, Mountain View, CA, UNITED STATES

Vogel, Kurt, Palo Alto, CA, UNITED STATES

Krebber, Claus, Mountain View, CA, UNITED STATES

Maxygen, Inc., Redwood City, CA (U.S. corporation) PATENT ASSIGNEE(S):

> NUMBER KIND DATE ----- ------

PATENT INFORMATION: US 2002127623 A1 20020912 US 2001-920607 A1 20010731 APPLICATION INFO.:

A1 20010731 (9)

NUMBER DATE ------

US 2000-222056P 20000731 (60) PRIORITY INFORMATION:

US 2000-244764P 20001031 (60)

DOCUMENT TYPE: Utility

FILE SEGMENT: APPLICATION

LEGAL REPRESENTATIVE: LAW OFFICES OF JONATHAN ALAN QUINE, P O BOX 458,

ALAMEDA, CA, 94501

NUMBER OF CLAIMS: 130 EXEMPLARY CLAIM: 1

7 Drawing Page(s) NUMBER OF DRAWINGS:

LINE COUNT: 6877

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

Methods for sensing test stimuli using arrays of biopolymers are provided. Libraries of biopolymers, such nucleic acid variants, and expression products encoded by nucleic acid variants are provided. Reusable library arrays, and methods for their use are provided.

ANSWER 2 OF 9 PCTFULL COPYRIGHT 2002 Univentio ACCESSION NUMBER: 2001092523 PCTFULL ED 20020826

TITLE (ENGLISH): NOVEL HUMAN POLYNUCLEOTIDES AND POLYPEPTIDES ENCODED

THEREBY

TITLE (FRENCH): NOUVEAUX POLYNUCLEOTIDES HUMAINS ET POLYPEPTIDES CODES

PAR CEUX-CI

INVENTOR(S): SHIMKETS, Richard, A.; LEACH, Martin, D.

CURAGEN CORPORATION; SHIMKETS, Richard, A.; LEACH, PATENT ASSIGNEE(S):

Martin, D.

DOCUMENT TYPE: Patent

PATENT INFORMATION:

DESIGNATED STATES

NUMBER KIND DATE ------

WO 2001092523 A2 20011206 AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR

CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW GH GM KE LS MW MZ SD SL SZ TZ UG ZW AM AZ BY KG KZ MD RU TJ TM AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE TR BF BJ

CF CG CI CM GA GN GW ML MR NE SN TD TG

APPLICATION INFO .: WO 2001-US10836 A 20010529 PRIORITY INFO.:

US 2000-60/206,132 20000530 US 2000-60/228,716 20000829

ABEN The present invention provides ORFX, a novel isolated polypeptide, as well as a polynucleotide encoding ORFX and antibodies that immunospecifically bind to ORFX or any derivative, variant, mutant, or fragment of the ORFX polypeptide, polynucleotide or antibody. The invention additionally provides methods in which the ORFX polypeptide, polynucleotide and antibody are used in detection and treatment of a broad range of pathological states, as well as to other uses.

ABFR La presente invention concerne le polypeptide ORFX, nouveau polypeptide isole, ainsi qu'un polynucleotide codant pour le polypeptide ORFX et des anticorps qui se fixent de facon immunospecifique a ORFX ou a n'importe quel derive, variant, mutant ou fragment de ce polypeptide ORFX, de ce polynucleotide ou de cet anticorps. Cette invention concerne aussi des techniques dans lesquelles le polypeptide ORFX, le polynucleotide et l'anticorps sont utilises pour detecter et traiter un grand nombre d'etats pathologiques, ainsi que d'autres utilisations.

ANSWER 3 OF 9 CAPLUS COPYRIGHT 2002 ACS L42000:117169 CAPLUS ACCESSION NUMBER: DOCUMENT NUMBER: 132:162810 TITLE: Cloning of genes for L-lysine-2-oxoglutarate 6-aminotransferase and piperidine-6 -carboxylate dehydrogenase from Flavobacterium lutescens and use of the genes for production of L-homoglutamic acid INVENTOR(S): Fujii, Tadashi; Narita, Takao; Nakata, Kuniho; Agematu, Hitosi; Tsunekawa, Hiroshi; Isshiki, Kunio; Yoshioka, Takeo Mercian Corp., Japan PATENT ASSIGNEE(S): PCT Int. Appl., 62 pp. SOURCE: CODEN: PIXXD2 DOCUMENT TYPE: Patent Japanese LANGUAGE: FAMILY ACC. NUM. COUNT: PATENT INFORMATION: KIND DATE PATENT NO. APPLICATION NO. DATE --------------_____ 20000217 WO 1999-JP4197 19990804 WO 2000008170 A1 W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG CA 2337981 AA 20000217 CA 1999-2337981 19990804 AU 9950642 A1 20000228 AU 1999-50642 19990804 EP 1999-935047 EP 1103612 Α1 20010530 19990804 AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO PRIORITY APPLN. INFO.: JP 1998-232382 A 19980805 JP 1999-182362 A 19990628 WO 1999-J9 990419W 19990804 WO 1999-JP4197 W 19990804 AB The genes encoding L-lysine-2-oxoglutarate 6-aminotransferase (LAT) and piperidine-6-carboxylate (P6C) dehydrogenase are isolated from Flavobacterium lutescens strain IFO 3084 and used for the transformation of F. lutescens to increase the yield of L-homoglutamic acid. LAT and P6C dehydrogenase are comprised of 491 and 510 amino acids, resp. Transformation of F. lutescens with the gene for LAT or P6C dehydrogenase increased the yield of L-homoglutamic acid by 1.5-2 folds. REFERENCE COUNT: 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT ANSWER 4 OF 9 CAPLUS COPYRIGHT 2002 ACS

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L4 ANSWER 4 OF 9 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1980:195215 CAPLUS
DOCUMENT NUMBER: 92:195215
TITLE: Enzyme of pipecolate metabolism. Studies on the question of regional piperidine synthesis in the mouse brain
AUTHOR(S): Garweg, G.; Von Rehren, D.; Hintze, U.
CORPORATE SOURCE: Anat. Inst., Univ. Hamburg, Hamburg, Fed. Rep. Ger.
SOURCE: Verhandlungen der Anatomischen Gesellschaft (1979), Volume Date 1978, 73(2), 1051-2
```

CODEN: VHAGAS; ISSN: 0066-1562

DOCUMENT TYPE: LANGUAGE:

Journal German

The distribution of .DELTA.1-pyrrolin-2-carboxylate reductase, L -pipecolate dehydrogenase, and .DELTA.1-piperideine-6-

carboxylate dehydrogenase activities in various regions of mouse brain was detd. A marked activity difference, with the max. conversion rate occurring in the prosencephalon and a lack of activity in cerebellum and medulla spinalis, was obsd. only for pyrrolin-2-carboxylate reductase. The expression of region-specific biogenesis of pipecolic acid in mouse brain was in between that previously reported for dog and monkey. contrast to them, the distribution of pipecolate dehydrogenase and piperideine-6-carboxylate dehydrogenase in mouse brain showed an extensive, equal distribution in all areas of the brain.

ANSWER 5 OF 9 CAPLUS COPYRIGHT 2002 ACS L4

ACCESSION NUMBER: 1972:55563 CAPLUS

DOCUMENT NUMBER:

76:55563

TITLE: AUTHOR (S): Pipecolic acid Rodwell, Victor W.

CORPORATE SOURCE:

Dep. Biochem., Purdue Univ., Lafayette, Indiana, USA

SOURCE:

Methods Enzymol. (1971), Volume 17, Issue Pt. B, 174-88. Editor(s): Colowick, S. P. Academic: New

York, N. Y. CODEN: 18HWA8

DOCUMENT TYPE: Conference LANGUAGE: English

Improved methods are given for synthesis of DL-pipecolic acid (I), with 2 methods for the resolution of I into D- and L-forms. In a new procedure, L-pipecolic acid (II) is obtained from fresh green beans (Phaseolus vulgaris). Phys. and chem. properties of I and II are given. Spectra are given (300-650 m.mu.) for the adducts of various imino acids with ninhydrin. When paper chromatograms are sprayed with ninhydrin in EtOH or acetone, the initial color with I is purple, like amino acids. On standing (particularly if collidine is present) the color changes to yellow-brown. If Cd acetate is added to the ninhydrin reagent, .alpha.-amino acids give red colors. The I color remains royal purple, providing a spot test for I. The purification and assay of II-dehydrogenase from Pseudomonas putida P2 (ATCC 25.571) are described. Properties of the enzyme are described.

ANSWER 6 OF 9 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER:

1967:112374 CAPLUS

DOCUMENT NUMBER:

66:112374

TITLE:

SOURCE:

Studies on the electron transport particle of

Pseudomonas P2 and purification of pipecolic acid

dehydrogenase

AUTHOR(S):

Baginsky, Marietta L.

CORPORATE SOURCE:

Univ. of California, San Francisco, CA, USA

(1967) 170 pp. Avail.: 65-4894

From: Diss. Abstr. B 1967, 27(7), 2268

DOCUMENT TYPE:

Dissertation

LANGUAGE:

English

AB Unavailable

ANSWER 7 OF 9 CAPLUS COPYRIGHT 2002 ACS ACCESSION NUMBER: 1967:513926 CAPLUS

DOCUMENT NUMBER:

67:113926

TITLE:

Metabolism of pipecolic acid in a Pseudomonas species.

V. Pipecolate oxidase and dehydrogenase Baginsky, Marietta L.; Rodwell, Victor W.

CORPORATE SOURCE:

Sch. of Med., Univ. of California, San Francisco, CA,

USA

SOURCE:

LANGUAGE:

AUTHOR (S):

J. Bacteriol. (1967), 94(4), 1034-9

CODEN: JOBAAY

DOCUMENT TYPE:

Journal English

cf. CA 65: 7493h. Oxidn. of pipecolate to .DELTA.1-piperideine-6carboxylate is catalyzed by pipecolate oxidase, an inducible,

membrane-bound dehydrogenase assocd. with the electron transport components of P. putida P2. From the oxidase a smaller particle contg. FAD and cytochrome b was obtained, but it was not able to catalyze electron transfer to O or to cytochrome c. Certain properties of the L-pipecolate dehydrogenase (I) an

FAD-flavoprotein, are reported. Neither O nor mammalian cytochrome c served as electron acceptors for pipecolate oxidn. by I. The apparent Km for L-pipecolate was 1.7 .times. 10-2M. 17 references.

L4 ANSWER 8 OF 9 DGENE (C) 2002 THOMSON DERWENT

ACCESSION NUMBER: AAY80510 Protein DGENE

TITLE: L-homoglutamic acid production gene, isolated from

Flavobacterium lutescens is used for production of transformants with enhanced conversion of lysine to

L-homoglutamic acid.

INVENTOR: Fujii T; Narita T; Nakata K; Agematu H; Tsunekawa H; Isshiki

K; Yoshioka T

PATENT ASSIGNEE: (SAOC) MERCIAN CORP.

PATENT INFO: WO 2000008170 A1 20000217 62p

APPLICATION INFO: WO 1999-JP4197 19990804 PRIORITY INFO: JP 1998-232382 19980805 JP 1999-182362 19990628

DOCUMENT TYPE:

Patent

LANGUAGE: OTHER SOURCE: Japanese

OTHER SOURCE: 2000-195579 [17]
AB This is the sequence of the piperidine-6-

carboxylate dehydrogenase protein from Flavobacterium

lutescens which is involved in the production of L-homoglutamic acid from L-lysine. The corresponding gene is capable of restoring L-homoglutamic acid production in mutants of F. lutescens lacking this ability. L-homoglutamic acid is used as a synthetic intermediate for drug

synthesis including methotrexate.

L4 ANSWER 9 OF 9 DGENE (C) 2002 THOMSON DERWENT

ACCESSION NUMBER: AAZ91051 DNA DGENE

TITLE: L-homoglutamic acid prod

L-homoglutamic acid production gene, isolated from Flavobacterium lutescens is used for production of transformants with enhanced conversion of lysine to

L-homoglutamic acid.

INVENTOR: Fujii T; Narita T; Nakata K; Agematu H; Tsunekawa H; Isshiki

K; Yoshioka T

PATENT ASSIGNEE: (SAOC) MERCIAN CORP.

PATENT INFO: WO 2000008170 A1 20000217 62p

APPLICATION INFO: WO 1999-JP4197 19990804 PRIORITY INFO: JP 1998-232382 19980805

JP 1999-182362 19990628

DOCUMENT TYPE: Patent LANGUAGE: Japanese

OTHER SOURCE: 2000-195579 [17]

AB This sequence represents the gene encoding the Flavobacterium lutescens piperidine-6-carboxylate

dehydrogenase gene which is involved in the production of L-homoglutamic acid from L-lysine. The gene is capable of restoring L-homoglutamic acid production in mutants of F. lutescens lacking this ability. L-homoglutamic acid is used as a synthetic intermediate for drug synthesis including methotrexate.